Neonatal alloimmune thrombocytopenia (NAITP or NAIT or NAT), or feto-maternal alloimmune thrombocytopenia (FMAITP or FMAIT)

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- A Current working theory is that Lovenox may have caused a slow low-level immunoresponse maternally where IgG and other antibodies were building up but remained relatively "clinically" asymptomatic. No blood tests were carried out to monitor such emerging conditions. It is well known that heparin-induced thrombocytopenia can occur and can be easily diagnosed and would have been symptomatic to the mother. However it remains to be determined (or found in tests performed by Aventis) if LMWH (low molecular weight heparin) is immunogenic to a lesser, subclincal manner. If so, altered levels of IgG could have been transferred to the fetus while the mother remained asymptomatic. This would be an insidious drug effect for the fetus, which would have remained relatively asymptomatic as well.

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- Maternal IgG is important since they are the only antibodies which traverse the placental barrier and are able to enter fetal circulation. The fetal/neonatal immune system is immature until the first several days following birth, so the only IgG source found in the newborn is from the mother. Normal IgG present in the fetus is an evolutionary protection for the fetus against infection etc. during gestation. However, excessive fetal IgG levels can bind to fetal platelet blood cells and be taken out of fetal circulation, thereby causing thrombocytopenia. The pro/anti coagulation balance (haemostasis) is then thrown out of balance and fetal bleeding and clotting ensues. Standard therapy for severe NAIT including transfusions of IVIG and platelets was carried out and found to be beneficial for Savannah; which more or less confirmed the IgG as the causative agent, where the over abundance of the infused IgG was able to swamp the spleen's IgG receptors and stop the fetal clearance of platelet-IgG complexes from the fetal circulation; the platelet infusion therapy aided in building the platelet count back towards normal.

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- The neonatal hematologist (Weil deposition) carried out many tests (Wisconsin tests etc), common etiologies were ruled out and the NAIT was concluded to be idiopathic. Many cases such as these can remain etiologically unsolved (Weil). This would be consistent with a possible drug effect causing the thrombocytopenia and being overlooked as the cause of the NAIT. Dr. Weil was curious about the positive indirect but negative direct Coombs test results. This conforms with our hypothesis that free antibodies circulating in the blood serum were present maternally and transferred to the fetus.

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- The remaining question is why the IgG was elevated maternally, as suggested by the positive Coombs test. Either due to the drug or due to the maternal status ie. a hypercoagulatory condition where prior maternal PVT events were evident and being treated prophilactically.

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- A simple test would be to carry out an indirect Coombs test before and after Lovenox administration to Janelle to see if IgG became elevated post-dosing and if extended dosing was necessary to produce a positive Coombs test. This still would not

take into consideration the effects of the pregnancy; however it would show a drug effect that would have contributed to the elevated maternal IgG when not pregnant.

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- The advantage when performing this in Janelle is that it would prove that the drug was responsible for an elevated Coombs test in her particular case. It would define a condition where an asymptomatic (subclinical) condition arose where IgG levels were occurring, and if in a pregnant individual may cause fetal exposure to IgG over extended amount of time causing thrombocytopenia.

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- Lovenox was not expected to be given (and was never tested) for times greater than 14 days. Maybe low-level heparin-induced effects are known but not discussed by company since subclinical.

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- "Subclinical" features of an immune response of this type can be devastating in a pregnancy situation. Apparently no pregnancy studies were undertaken. Company should have not allowed pregnant individuals to take lovenox, and certainly not past the labeling duration of 14 days.

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- No hematological tests (indirect Coombs etc.) were undertaken to monitor for changes in maternal IgG, since asymptomatic. Company should have recommended indirect Coombs tests to be undertaken to detect elevated maternal immune response, in addition to the now recommended Xa screening (LMWH specifically blocks Xa, so the Xa test is recommended and not the INR (PT or APTTa)). The company may have been reluctant to recommend "testing" since a major selling point is "no monitoring is necessary for Lovenox" – Kahn deposition.

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- Scrutiny of all immunological tests carried out in animals from the manufacturer to study immunogenic effects of lovenox (enoxaparin), particularly IgG, should be undertaken. This may lead to the dosing level and duration recommendations for Lovenox of exposure to 14 days or less. The reasoning for these limitations may have bearing to the present case.

The effect of Lovenox residing in the maternal circulation can induce maternal IgG changes, and these drug induced changes altering IgG levels are transferred to the fetal circulation, since IgG does cross the placental barrier. It is the effect of Lovenox administration which causes the thrombocytopenia in the neonate via the effect on maternal IgG.

Apparently no substantial clinical tests were conducted in pregnant individuals, and no long term studies were carried out past 2 weeks to warrant extended dosing past that time. Pregnancies naturally involve substantial pro- and anti-coagilative alterations, so not to investigate these coagulative states during pregnancy as they relate to this LMWH anticoagulant and not to discuss this more fully to the health care providers and/or contraindicate their use and/or require monitoring if used over extended periods outside of studied conditions seems to be courting trouble on its face.

If a large molecular weight compound is not synthetically produced but instead is purified from an animal or human source, impurities will always be present to some degree. Examples of large molecular weight compounds used as drugs are Insulin (bovine or equine derived) and hGH (animal derived) extracts, both of which contain impurities. hGH has been synthetically produced so as to eliminate viral contaminants causing rare but fatal neurological disease occuring when derived hGH is used. Lovenox is not synthetically produced, so the raw materials and the process of extraction will determine its degree of suitability for use as a drug product. Contaminants can range from a mix of proteins to exogenous compounds, both of which can have a multitude of untoward effects, including immunogenic and toxic effects.

Hemostasis is a complex interplay and is best discussed by a hemotologist. In general cascades of factors in the body provide the balance between the pro- and anti-coagulant states necessary for proper circulation and health. Focusing on the IgG effects (as discussed in my earlier more detailed discussion sent out as a separate file) the resultant neonatal thrombocytopenia may have developed as described previously.